Clinical Biochemistry in Toxicology

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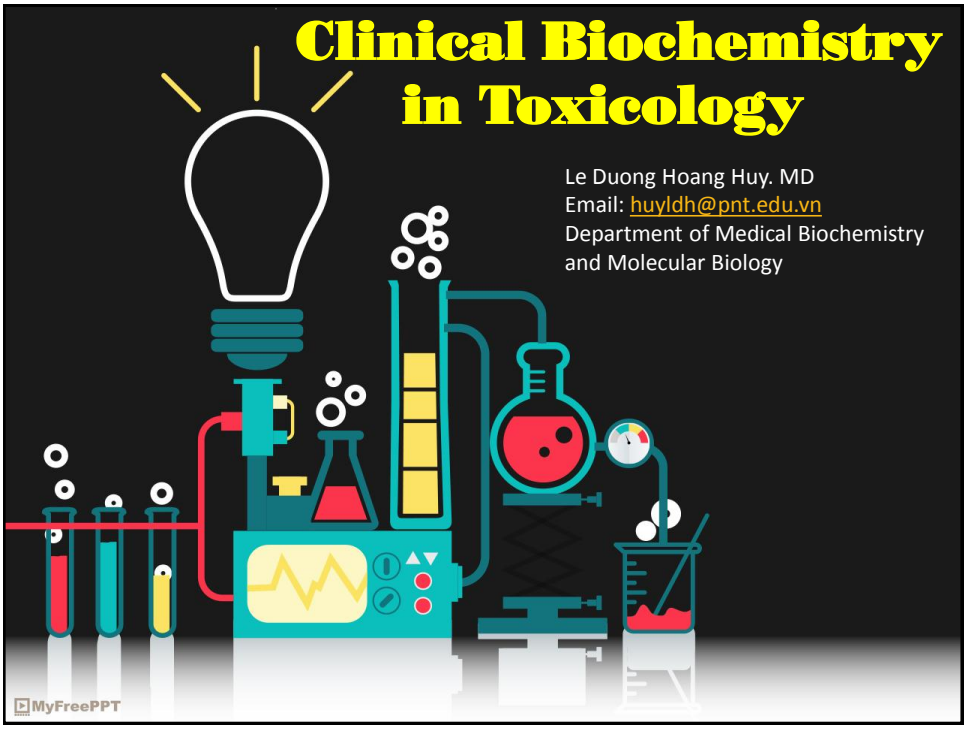


Objectives

1. List the most common poisons.
2. Describe the circumstances in which poisoning occurs and the factors that influence the toxicity of a substance.
3. Select appropriate laboratory investigations based on clinical features and history
4. Describe how common poisons are metabolied in body.

Contents

- Definition of toxicology, poisons, poisoning.
- Laboratory investigation of poisoning
- Management of the poisoned patient
- Toxicology of some common compounds

Refference:

- **Dr Nessar Ahmed**, Clinical Biochemistry, Oxford.
- **Michael Lieberman,** Marks' **Basic Medical Biochemistry,** a Clinical Approach, Fourth Edition
- **Harrison's Principle of internal medicine 19th edition.**

Toxicology

- **Toxicology** is the scientific study of **poisons** and **poisoning**, and has applications in many areas, including the industrial, agricultural, veterinary, environmental, forensic, and medical fields.

- All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy.

  Paracelsus (1493-1541)
  The Father of Modern Toxicology

Toxicology

- **Clinical biochemistry in toxicology** = identification and measurement of the concentrations of poisons or biomarkers of their effects, in body fluids, tissues, and sometimes other materials.

Types of poisons and poisoning

- Poisons?
- Poisoning?

Types of poisons and poisoning

Inorganic	Organic
Anions: include cyanide, fluoride, nitrite, and oxalate **Corrosives:** sulphuric acid, heavy metal salts **Metals:** iron, lead, and arsenic, … **Gases and volatiles** carbon monoxide	**Organic acids** **Toxins:** snake venom, biological compounds produced by plants, animals, bacteria, and fungi **Pesticides** **Drugs**

Clinical features of poisoning

- Neurological
- Respiratory
- Cardiovascular
- Gastrointestinal
- Eyes, skin, and muscle
- .....

Biochemical features of poisoning

- Disturbances in **acid-base balance, Nephrotoxicity, ischaemia** → metabolic acidosis.
- Metabolic alkalosis, respiratory acidosis, and respiratory alkalosis may also occur →Mixed
- Hyponatraemia Hypernatraemia
- Hypokalaemia Hyperkalaemia
- Hypocalcaemia
- Increased osmolar gap
- Urea and creatinine
- Raised transaminases
- Hypoglycaemia

Management of the poisoned patient

- Most poisoned patients will survive with supportive care :
  - ABC of resuscitation
  - Ventilatory support
  - Determine Hypotension
  - Control hypoxia, acidosis and arrhythmias
  - Use of **antidote**
    …

Antidotes are medicines that prevent the toxic effects of a specific poison or group of poisons

Poison	Antidote
Acetaminophen	Acetylcysteine
Anesthetics, local	Lipid emulsion (Fat Emulsion)
Aniline	Methylene blue
Anticholinesterases (i.e. organophosphates)	Atropine, Pralidoxime (2-PAM)
Antidepressants, Cyclic (TCAs)	Sodium bicarbonate, Lipid emulsion
Antidepressants, noncyclic (i.e., SSRIs, SNRIs, bupropion, venlafaxine, etc)	Sodium bicarbonate, Lipid emulsion
Arsenic	Dimaval
Benzodiazepines	Flumazenil
Beta-blockers	Atropine, Insulin, Calcium, Glucagon (adjunctive therapy only), Lipid emulsion
Black Widow spider	Black Widow spider antivenin (Antivenin Latrodectus Mactans)
Calcium channel blockers	Atropine, Insulin, Calcium, Lipid emulsion
Cyanide	Hydroxocobalamin (Cyanokit), Sodium thiosulfate
Digoxin	Atropine, Digoxin immune Fab
Ethylene glycol	Fomepizole, Pyridoxine, Sodium bicarbonate
Glycol Ethers	Fomepizole
Hydrofluoric acid burns	Calcium gluconate
Iron	Deferoxamine (Desferrioxamine)
Isoniazid	Pyridoxine
Lead	Dimaval
Mercury (inorganic or elemental)	Dimaval
Methanol	Fomepizole
Mushrooms, Hepatotoxic (i.e., Amanita phalloides)	Acetylcysteine
Mushrooms, Seizure-inducing (gyromitra or hydrazine-containing mushrooms)	Pyridoxine

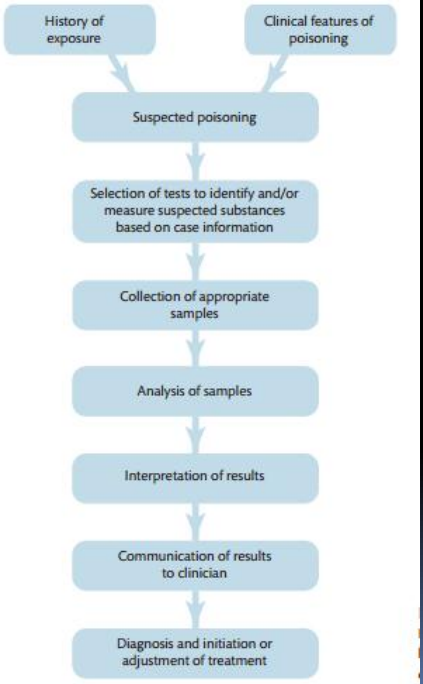
Nitrates	Methylene blue
Nitrites	Methylene blue
Opioids	Naloxone
Organophosphate insecticides	Atropine Pralidoxime (2-PAM)
Salicylates	Sodium bicarbonate
Sodium channel blocking drugs* (wide QRS)	Sodium bicarbonate, Lipid emulsion
Sulfonylurea (oral hypoglycaemic)	Octreotide

IWK Regional Poison Centre. Canada

Sodium channel blockers encompass many classes of drugs which can result in widening of the QRS and hypotension with toxicity. Examples of these drugs include: Amantadine, Carbamazepine, Chloroquine, Class IA antiarrythmics Class IC antiarrythmics , Citalopram, Cocaine, Cyclic antidepressants, Diltiazem, Diphenhydramine, Dimenhydrinate, Hydroxychloroquine, Loxapine, Orphenadrine, Phenothiazines, Propranolol, Propoxyphene, Quinine, Verapamil

Laboratory investigation of poisoning

- Qualitative analysis →diagnosis or identification of the poison
- Quantitative analysis→ monitoring treatment measurement



Flow diagram for the laboratory investigation of poisoning.

Laboratory investigation of poisoning

It might be expected that identifying the agent and the extent of exposure would be a prerequisite for treatment

How about in practice?

Laboratory investigation of poisoning

Investigation	Reason
Quantitative in blood or serum:	
Paracetamol	Antidote available
Salicylate	Specific treatment
Ethanol	Specific treatment and monitoring treatment when used as antidote
Carboxyhaemoglobin	Antidote available
Methaemoglobin	Antidote available
Iron	Antidote available
Digoxin	Antidote available
Lithium	Specific treatment
Theophylline	Specific treatment
Qualitative:	
Urine paraquat	Prognosis

Toxicology of specific compounds

- Carbon monoxide
- Ethanol
- Paracetamol (Acetaminophen)
- Salicylate
- Drugs of abuse

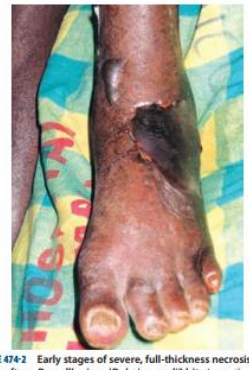
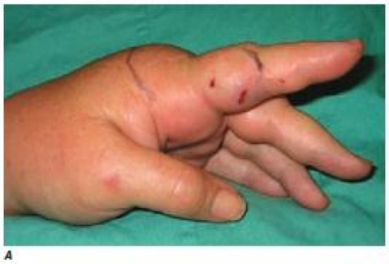
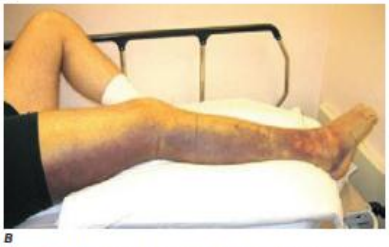


FIGURE 474-2 Early stages of severe, full-thickness necrosis 5 days after a Russell's viper (*Daboia russelii*) bite in southwestern India.



A



B

FIGURE 474-1 Northern Pacific rattlesnake (*Crotalus oreganus oreganus*) envenomations. *A.* Moderately severe envenomation. Note edema and early ecchymosis 2 h after a bite to the finger. ***B.*** Severe envenomation. Note extensive ecchymosis 5 days after a bite to the ankle.

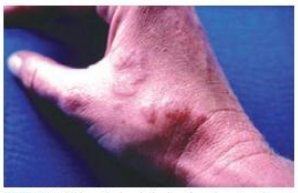


FIGURE 474-4 Rash on the hand of a diver from the spines of a bristleworm. *(Courtesy of Paul Auerbach, with permission.)*

FIGURE 475-2 Adult female human head louse (*Pediculus capitis*) on a nit (louse-egg) comb.

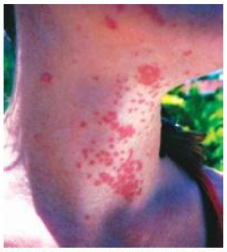


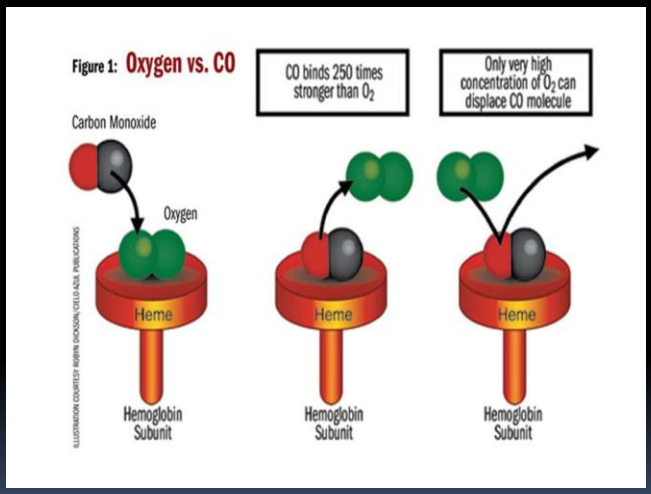
FIGURE 474-7 Erythematous, papular rash typical of seabather's eruption caused by thimble jellyfish and larval anemones.

FIGURE 475-1 Deer ticks (*Ixodes scapularis*, black-legged ticks) on a U.S. penny: larva (*below ear*), nymph (*right*), adult male (*above*), and adult female (*left*).

Carbon monoxide

- **Sources**:vehicles or malfunctioning gas appliances, smoke from fires, and cigarette smoke.
- **Symtoms**: headache, dizziness, nausea, malaise, and a flu-like feeling ➔ vague and non-specific ➔ acute, sub-acute, chronic.

Carbon monoxide



Carbon monoxide

- Features of **acute carbon monoxide poisoning** include metabolic acidosis, normal *P*O2 with reduced oxygen saturation, features of hypoxic damage to organs and tissues, for example kidney, skeletal muscle, and a high blood COHb.

Carbon monoxide

Table 1. Effects of COHb level in the blood of healthy subjects [adapted from WHO(1999)].

COHb (%)	Effect
< 2	Small decreases in work capacity
5	Decrease of oxygen uptake and exercise performance; decrements in neurobehavioral function
10	Shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessel
20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples
30	Decided headache; irritable; easily fatigued; judgement disturbed; possible dizziness; dimness of vision
40 – 50	Headache; confusion; collapse; fainting on exertion
60 – 70	Unconsciousness; intermittent convulsion; respiratory failure; death if exposure is long continued
80	Rapidly fatal

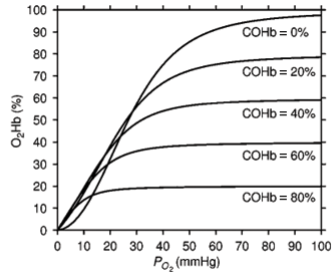
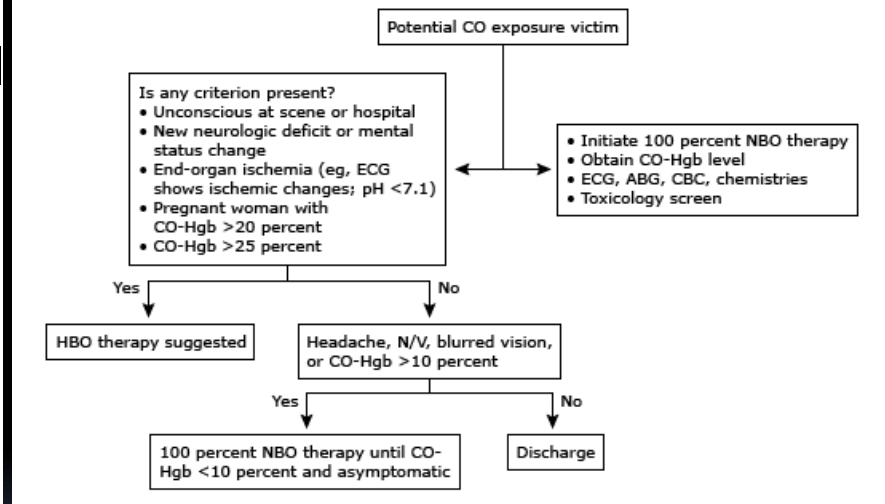


Figure 1. Dissociation curve of O_2 in the blood for several values of COHb.

Carbon monoxide

Reason for high carbon monoxide concentration in air	Exposure time	Blood carboxyhaemoglobin %	Toxic effects
City air	Continuous	<5	
Tobacco smoke	Intermittent	<10	
		10–20	Headache, nausea
Faulty boiler	Intermittent	20–50	Headache, nausea, weakness, impaired vision, fainting , vomiting, diarrhoea
Faulty boiler Car exhaust into sealed car	Hours Minutes	>50	Bradycardia, hypotension, respiratory depression, coma convulsions and death

Relationship between carbon monoxide exposure, blood carboxyhaemoglobin, and toxic effects. Note: heart or respiratory disease increase the susceptibility to carbon monoxide poisoning so that toxic effects are seen at lower COHb levels.



CO: carbon monoxide; ECG: electrocardiogram; CO-Hgb: carboxyhemoglobin; NBO: normobaric oxygen; HBO: hyperbaric oxygen; N/V: nausea and vomiting.

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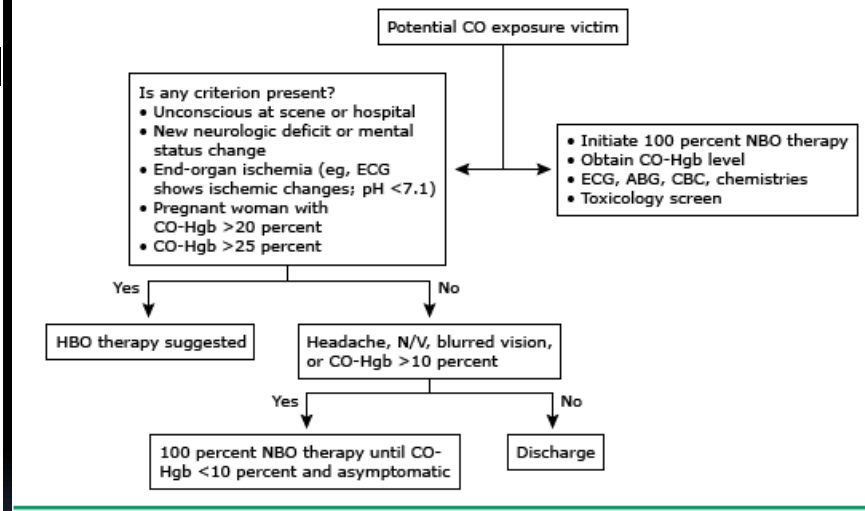

CO: carbon monoxide; ECG: electrocardiogram; CO-Hgb: carboxyhemoglobin; NBO: normobaric oxygen; HBO: hyperbaric oxygen; N/V: nausea and vomiting.

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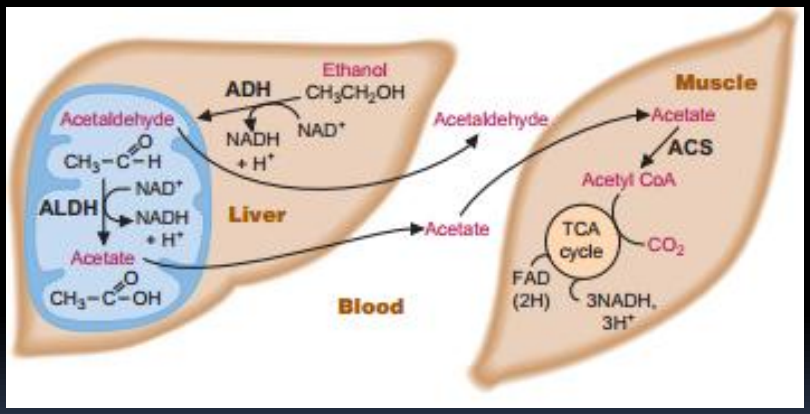
Ethanol

- CH_3CH_2OH
- Peak blood concentrations of ethanol occur 0.5–3 hours after ingestion .

Ethanol



The major route for metabolism of ethanol and use of acetate by the muscle.*ADH*, alcohol dehydrogenase; *ALDH*, acetaldehyde dehydrogenase; *ACS*, acetyl-CoA synthetase.

Ethanol

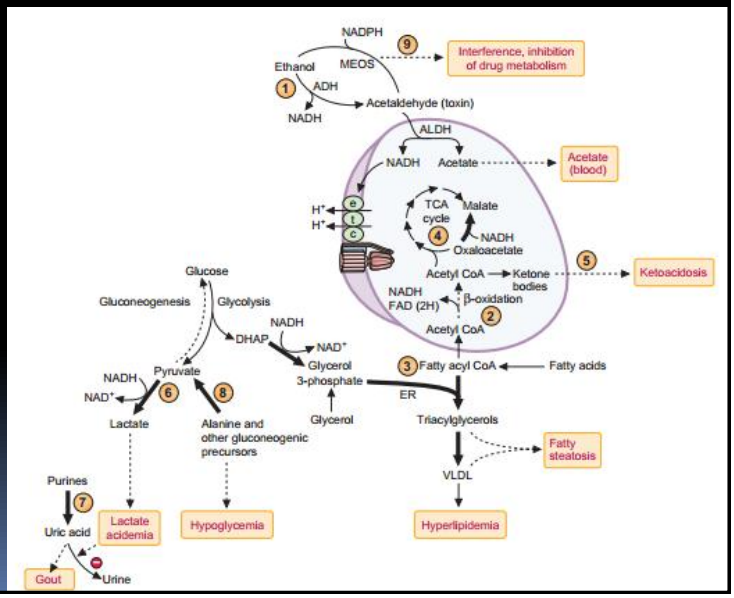
- Clinical features:a sense of enhanced well-being, dizziness, nystagmus, ataxia, dysarthria, nausea, vomiting, drowsiness, hypotension, hypothermia, respiratory depression, convulsions, and coma.
- Laboratory features: raised plasma osmolality, mild metabolic acidosis, ketosis, and hypoglycaemia

Ethanol

- *TOXIC EFFECTS OF ETHANOL METABOLISM:*
  - *Acute Effects of Ethanol Arising from the Increased NADH/NAD+ Ratio*
  - *Acetaldehyde Toxicity*
  - *Ethanol and Free Radical Formation*
  - *Hepatic Cirrhosis and Loss of Liver Function*

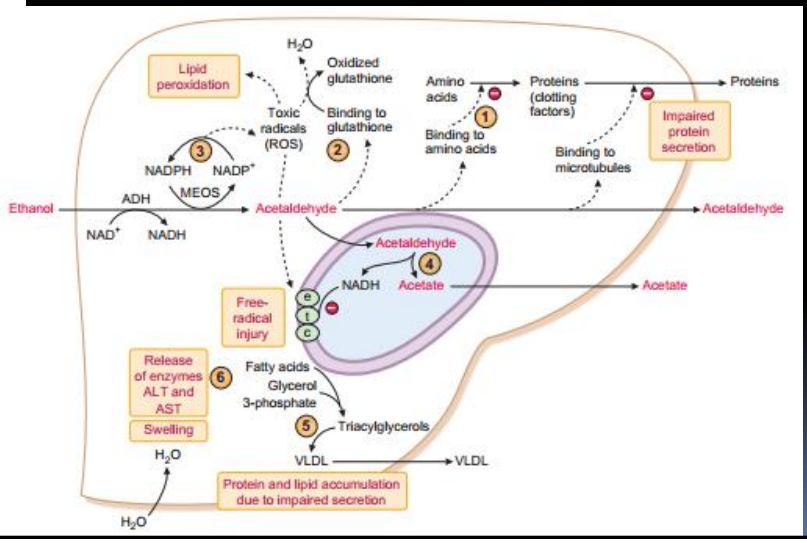
Ethanol

Acute Effects of Ethanol Arising from the Increased NADH/NAD+ Ratio



Ethanol

Acetaldehyde Toxicity



- Measurements from serum provide the most accurate determination of a patient's alcohol level.
- Alternative methods: breath analysis.

Ethanol

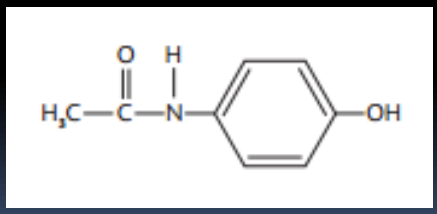
Clinical effects of blood alcohol concentration

Blood alcohol concentration	Clinical effects
20-50 mg/dL (4.4-11 mmol/L)	Diminished fine motor coordination
50-100 mg/dL (11-22 mmol/L	Impaired judgment; impaired coordination
100-150 mg/dL (22-33 mmol/L)	Difficulty with gait and balance
150-250 mg/dL (33-55 mmol/L)	Lethargy; difficulty sitting upright without assistance
300 mg/dL (66 mmol/L)	Coma in the non-habituated drinker
400 mg/dL (88 mmol/L)	Respiratory depression

Adapted from: Marx JA. Rosen's emergency medicine: concepts and clinical practice, 5th ed, Mosby, Inc., St. Louis 2002. p. 2513. Copyright © 2002 Elsevier.

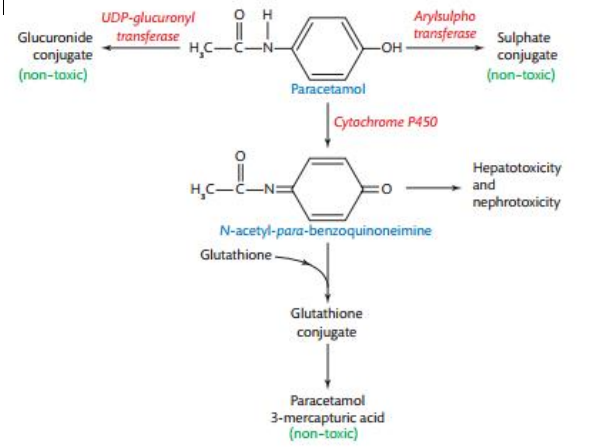
Paracetamol

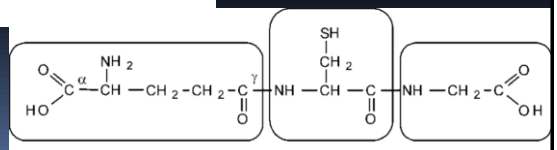
Peak blood concentrations occurring 1–2 hours after therapeutic ingestion.
In overdose the time to peak concentration is increased and may be as long as four hours



Paracetamol structure.

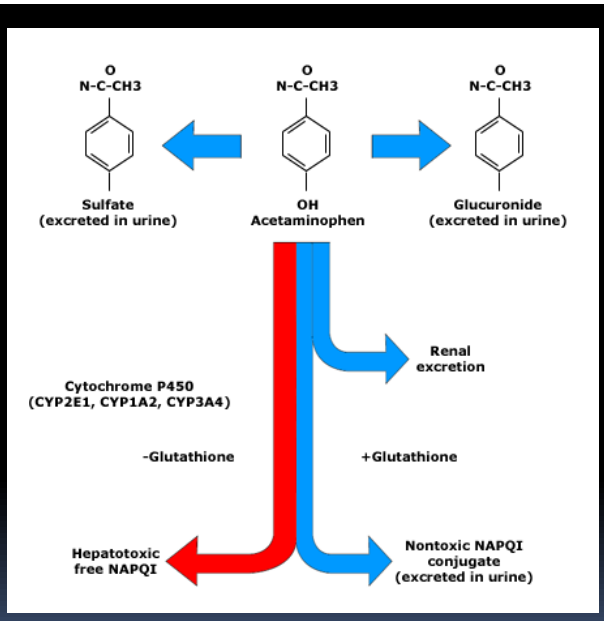
Paracetamol





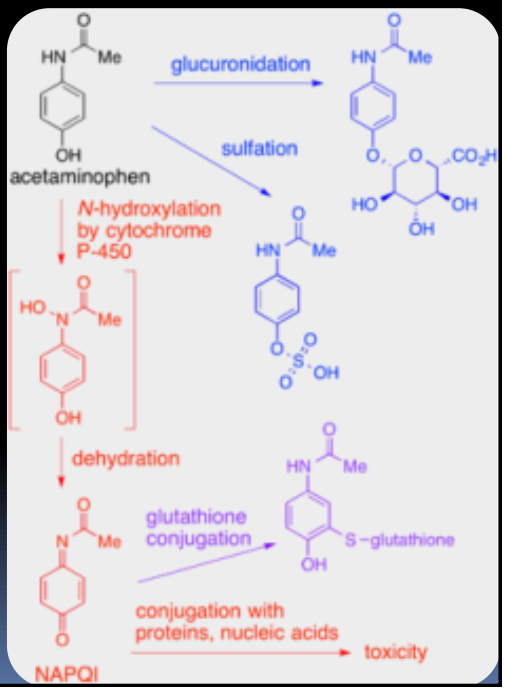
Glutathion

Glutamic acid Cysteine Glycine



Paracetamol

Paracetamol is metabolized in the liver to sulphate and glucuronide conjugates and the toxic metabolite NAPQI. The latter binds to thiol (-SH) groups



Paracetamol

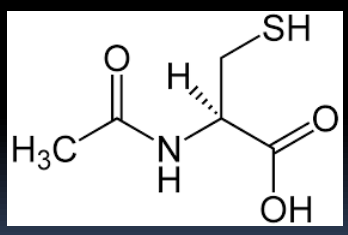
- The toxic effects of paracetamol overdose:
  + Delayed
  + Necrosis → Liver failure → death after 2–3 days if untreated
  + 15% of cases are complicated by acute renal failure

Paracetamol

- **Clinical features**: vomiting, abdominal pain, and jaundice.
- **Laboratory features**:raised serum alanine and aspartate aminotransferases, with peak activities occurring at 72–96 hours after the overdose, raised bilirubin, prolonged prothrombin time, haematuria, and raised serum creatinine.

Paracetamol

- N-acetylcysteine, given by intravenous infusion, prevents liver damage by supplying SH groups.



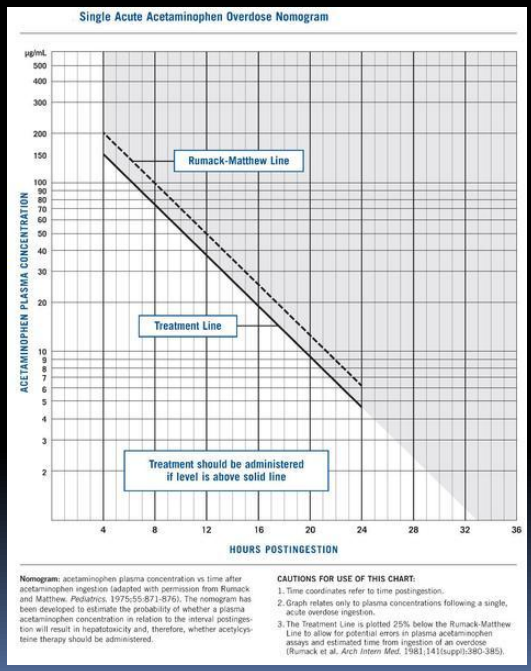
N-acetylcysteine

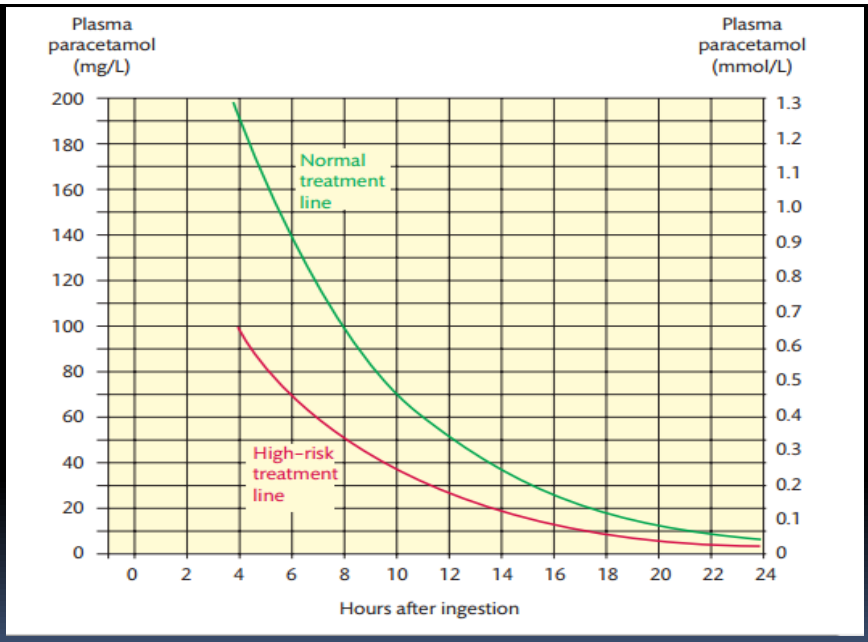
Paracetamol

- The risk of **hepatotoxicity** is related to the plasma concentration of paracetamol measured in samples collected at least four hours after ingestion.

Paracetamol

- The risk is higher if patients exposed:
  - Ethanol
  - Anticonvulsant drugs (carbamazepine and phenytoin)
  - Hepatitis Virus B or C



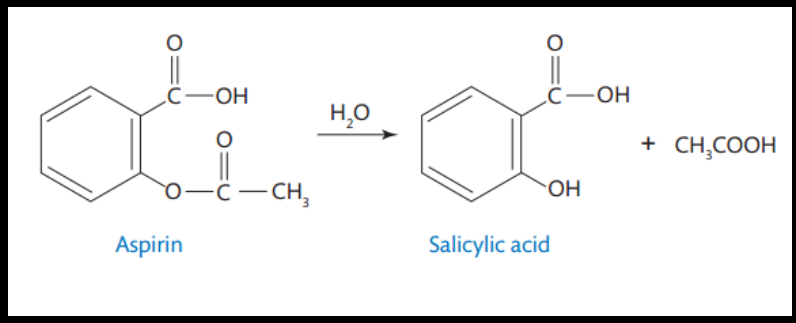


Nomogram for interpretation of serum paracetamol concentrations in cases of suspected toxicity

Case Study 1

- A 21-year-old female was brought to hospital by her boyfriend at 9 pm. He had gone out after they had an argument earlier that day and when he returned she was feeling sick and vomiting; she told him that she had taken two packets (16 tablets per pack) of paracetamol at about 3.30 pm. Blood was collected immediately for paracetamol, urea and electrolytes, creatinine, liver function tests, and prothrombin time. Her serum paracetamol concentration was 250 mg/L.
- Should she be given N-acetylcysteine to prevent liver damage? Explain your answer.

Salicylate



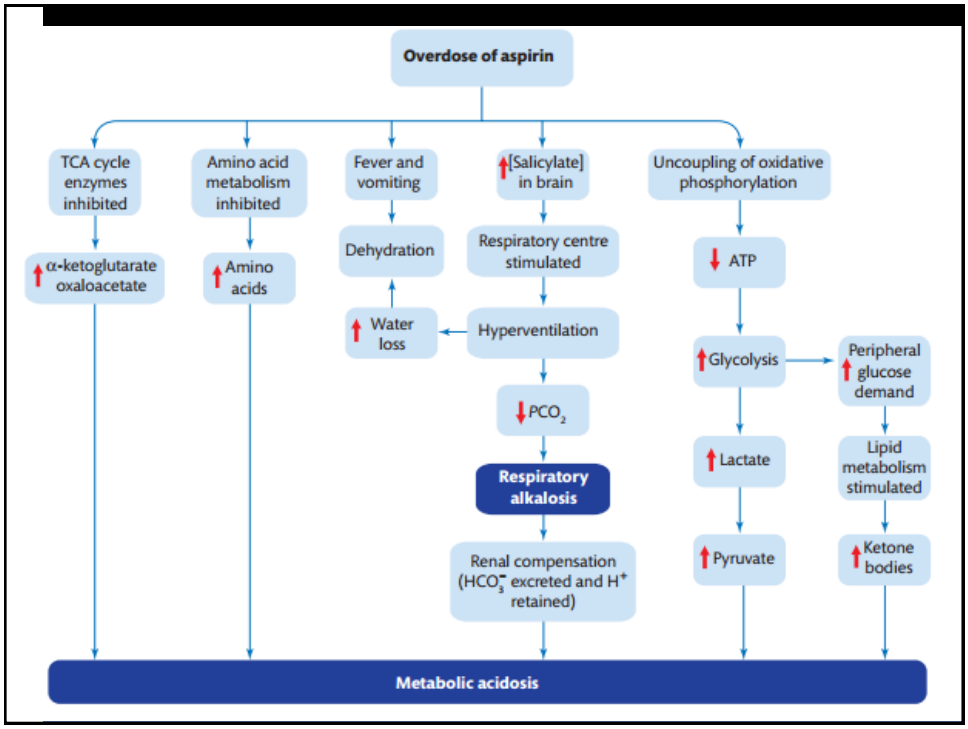
Aspirin is metabolized in the liver to salicylic acid commonly referred to as salicylate.

Salicylate

- Poisoning is common:
  - Oral overdose
  - Dermal absorption (psoriasis)
  - Buccal absorption

Salicylate

- Salicylate has direct effects on:
  - The inner ear
  - Gastrointestinal tract
  - Respiratory centre
  - Oxidative phosphorylation



Salicylate

- ***Key Points***
  Salicylate poisoning can cause a **mixed acid-base disorder**. A respiratory alkalosis due to the effect of salicylate on the respiratory centre is often accompanied by a severe metabolic acidosis due to increased production of acids.

Salicylate

- **Clinical features**: nausea and vomiting, vasodilatation, sweating, tinnitus, impaired hearing, pulmonary oedema, renal failure, convulsions, and arrhythmias.
- **Laboratory features**: a raised anion gap, acid-base disturbance (mixed respiratory alkalosis with metabolic acidosis), hypo- or hyperkalemia, hypoglycaemia, and increased prothrombin time.

Salicylate

- **Specific treatment:**
- Alkalinization of the urine with intravenous sodium bicarbonate when
  - plasma salicylate exceeds 350 mg/L in a child
  - plasma salicylate exceeds 450 mg/L in an adult
- Haemodialysis when
  - plasma salicylate is above 700 mg/L
- Intravenous glucose when severe poisoning
  - to avoid **neuroglycopenia**

Drugs of abuse

- 'Drugs of abuse' is a collective term used for several classes of drugs that are used for nonmedical purposes.

Drugs of abuse

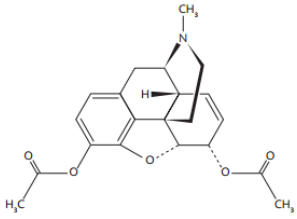


FIGURE 22.13
Heroin.

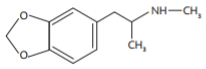


FIGURE 22.10
Methylenedioxymethamphetamine.

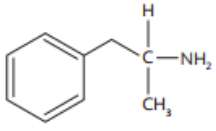


FIGURE 22.11
Amphetamine.

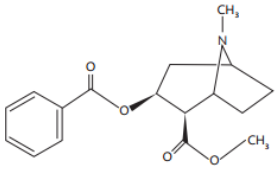


FIGURE 22.12
Cocaine.

Drugs of abuse

- Advantageous as drugs in urine:
- Higher concentrations than in blood
- Protein-free → simpler sample preparation
- Safer for laboratory staff

Drugs of abuse

- Urine concentrations do not relate closely to blood concentrations so quantitative analysis does not confer any benefit over qualitative analysis.

Drugs of abuse

- Confirm a diagnosis
- Confirm claims of drug
- Confirm compliance with abstinence agreements
- Investigate and differential diagnosis

- A 30-year-old man recently released from prison collapsed on arrival at his hostel, apparently drunk after going to a pub with friends.
- Examination in hospital showed a GCS of 7, bradycardia, hypotension, shallow breathing, and pinpoint pupils. A recent needle puncture mark was noted in his groin. He rapidly regained consciousness when given naloxone and subsequently recovered with supportive care.
- What toxicology tests would be appropriate?

- What is TRUE with regards to the metabolism of paracetamol and consequently its toxicology?

A. Paracetamol has a complex tricyclic structure that requires CYP metabolism prior to conjugative phase 2 metabolism.
B. Toxicity is mediated by NAPQI when it cannot be bound to intracellular glutathione.
C. Paracetamol is predominantly metabolised via CYP2E1
D. Paracetamol is predominantly metabolised via CYP3A4